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=> s insulin near5 purification
L1 0 FILE CAPLUS
L2 0 FILE MEDLINE
L3 0 FILE EMBASE
L4 0 FILE BIOSIS

TOTAL FOR ALL FILES
L5 0 INSULIN NEAR5 PURIFICATION

=> s insulin near 4 purification
L6 0 FILE CAPLUS
L7 0 FILE MEDLINE
L8 0 FILE EMBASE
L9 0 FILE BIOSIS

TOTAL FOR ALL FILES
L10 0 INSULIN NEAR 4 PURIFICATION

=> s insulin adj4 purification
L11 0 FILE CAPLUS
L12 0 FILE MEDLINE
L13 0 FILE EMBASE
L14 0 FILE BIOSIS

TOTAL FOR ALL FILES
L15 0 INSULIN ADJ4 PURIFICATION

```
=> s purification adj2 insulin
L16           0 FILE CAPLUS
L17           0 FILE MEDLINE
L18           0 FILE EMBASE
L19           0 FILE BIOSIS

TOTAL FOR ALL FILES
L20           0 PURIFICATION ADJ2 INSULIN

=> s insulin and purification
L21        2092 FILE CAPLUS
L22        4928 FILE MEDLINE
L23        1482 FILE EMBASE
L24        1539 FILE BIOSIS

TOTAL FOR ALL FILES
L25       10041 INSULIN AND PURIFICATION

=> s l25 and antibody
L26         320 FILE CAPLUS
L27         901 FILE MEDLINE
L28         254 FILE EMBASE
L29         212 FILE BIOSIS

TOTAL FOR ALL FILES
L30        1687 L25 AND ANTIBODY

=> s l30 and impurity
L31           4 FILE CAPLUS
L32           1 FILE MEDLINE
L33           2 FILE EMBASE
L34           0 FILE BIOSIS

TOTAL FOR ALL FILES
L35           7 L30 AND IMPURITY

=> dup rem
ENTER L# LIST OR (END):l35
PROCESSING COMPLETED FOR L35
L36           6 DUP REM L35 (1 DUPLICATE REMOVED)

=> d l36 ibib abs total

L36  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2000:386308  CAPLUS
DOCUMENT NUMBER:          133:140041
TITLE:                    Isolation, properties and immunoaffinity
                          chromatography of proinsulin impurities in
                          commercial porcine insulin preparations
AUTHOR(S):                Moroz, I. N.; Ermolenko, M. N.; Pryadko, A. G.;
                          Levchenko, V. K.; Senchuk, Yu. V.; Svirid, V. D.;
                          Sviridova, O. V.; Didorenko, A. I.; Petrov, P. T.;
                          Tsarenkov, V. M.
CORPORATE SOURCE:         Inst. Bioorg. Khim., NAN Belarusi, Belarus
SOURCE:                   Vestsi Natsyyanal'nai Akademii Navuk Belarusi, Seryya
                          Khimichnykh Navuk (2000), (1), 72-78
                          CODEN: VNBNFX; ISSN: 1561-8331
PUBLISHER:                Belaruskaya Navuka
DOCUMENT TYPE:            Journal
LANGUAGE:                 Russian
AB   Porcine proisulin has been isolated from a secondary fraction of the
     industrial process of insulin purifn. The native
     prohormone and its damaged mol. form with the cleavaged Arg63-Gly64 bond
     prevailed in the isolated prepn. According to the quality gradation
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accepted in immunoassay technol., the purified proinsulin met the following requirements: suitable for labeling, immunization and std. prepn. Murine monoclonal **antibodies** to proinsulin have been obtained and characterized. A purified product' of one of the clones was immobilized on CNBr-activated Sepharose. An interaction of the isolated proinsulin and the prohormone in **insulin** fractions with the immunoaffinity column has been studied. In principle, the possibility was shown for contaminant proinsulin to be completely removed from com. **insulin** prepns. by immunoaffinity chromatog.

L36 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:62416 CAPLUS
DOCUMENT NUMBER: 108:62416
TITLE: Treatment of biological and pharmaceutical products adsorbed on a solid phase with virus and pyrogen inactivating agents
INVENTOR(S): Chandra, Sudhish; Feldman, Fred
PATENT ASSIGNEE(S): Armour Pharmaceutical Co., USA
SOURCE: Eur. Pat. Appl., 26 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 197554	A2	19861015	EP 1986-104849	19860409
EP 197554	A3	19870325		
EP 197554	B1	19900725		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
US 4673733	A	19870616	US 1985-722561	19850411
AU 8655960	A1	19861106	AU 1986-55960	19860409
AU 580402	B2	19890112		
CA 1262682	A1	19891107	CA 1986-506180	19860409
AT 54828	E	19900815	AT 1986-104849	19860409
DK 8601617	A	19861012	DK 1986-1617	19860410
JP 61275210	A2	19861205	JP 1986-82425	19860411
JP 05078532	B4	19931029		

PRIORITY APPLN. INFO.: US 1985-722561 19850411
EP 1986-104849 19860409

AB Viruses and pyrogens in pharmaceutical products are inactivated by adsorbing the product onto a solid phase, which is washed with a virus deactivating or depyrogenating agent. **Impurities** and residual wash are removed from the solid phase, and the product is recovered. Blood products may thus be freed of hepatitis B virus. The plasma fraction used for isolating prothrombin complex was spiked with Sindbi's or vesicular stromatitis virus (VSV). The plasma was absorbed onto DEAE-Sephadex and treated with 2% Triton X-100 to inactivate the virus. The ion exchanger was washed with a citrate buffer and the prothrombin complex was eluted. In a control, the Triton X-100 wash was not used. The Triton X-100 treatment decreased virus activities of Sindbis and VSV by 2.07 .times. 103 and 8.45 .times. 104 times compared to controls, in vitro.

L36 ANSWER 3 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 81036331 EMBASE
DOCUMENT NUMBER: 1981036331
TITLE: The immunogenicity of **insulin** preparation. **Antibody** levels before and after transfer to highly purified porcine **insulin**.
AUTHOR: Heding L.G.; Larsson Y.; Ludvigsson J.
CORPORATE SOURCE: Novo Res. Inst., DK-2880 Bags Vaerd, Denmark
SOURCE: Diabetologia, (1980) 19/6 (511-515).

CODEN: DBTGAJ
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
003 Endocrinology
006 Internal Medicine
026 Immunology, Serology and Transplantation
030 Pharmacology
LANGUAGE: English

AB Ninety-two **insulin**-dependent diabetics (aged 4-20 years, mean .+-. SD: 13 .+-. 4) with a duration of diabetes from 2 to 17 years (7 .+-. 3) were transferred from Lente or NPH (5 x crystallised **insulin**) to Monotard **insulin** (highly purified **insulin**). Total serum immunoreactive **insulin** levels and concentrations of **antibodies** against **insulin**, porcine proinsulin, a-component and pancreatic polypeptide were determined prior to [I] and at a mean of 220 [II], 460 [III], 830 [IV], and 1170 [V] days after the change. All but two subjects had **insulin antibodies** (IgG) at the start, with a mean value of 2864 .mu.U/ml. There was a significant fall in the mean **insulin antibody** level between [I] and [II] to 2165 .mu.U/ml ($p < 10-7$), followed by an increase between [II] and [III] whereafter a slight decrease was observed being significant between [III] and [IV], as well as between [IV] and [V] ($p < 0.05$); some patients showed a constant fall over the entire period, while others showed fluctuations. Total serum **insulin** showed a similar pattern, with a mean value of 1141 .mu.U/ml at [I] declining to 522 .mu.U/ml at [V]. The percentage fall between [I] and V] was treater (54%) than that in the **insulin** atibodies (30%). **Antibodies** against a-component, proinsulin and pancreatic polypeptide were present in 96%, 72% and 41% of the patients respectively before the change in therapy. There was a decline in these **antibodies** between each sampling (p values between < 10-3 and 10-8) and, at the end of the investigation **antibodies** against a-component were above the detection limit in only 4 patients, and none of the patients showed **antibodies** against proinsulin or pancreatic polypeptide. Thus, removal of the **impurities**, including the hormonal contaminants of **insulin**, leads to a slow fall in **antibodies** to **insulin** and a much faster disappearance of **antibodies** against a-component, proinsulin and pancreatic polypeptide.

L36 ANSWER 4 OF 6 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 79014681 MEDLINE
DOCUMENT NUMBER: 79014681 PubMed ID: 694712
TITLE: Circulating **antibodies** in diabetics treated with conventional and purified **insulins**.
AUTHOR: Klaff L J; Vinik A I; Berelowitz M; Jackson W P
SOURCE: SOUTH AFRICAN MEDICAL JOURNAL, (1978 Jul 22) 54 (4) 149-53. Journal code: 0404520. ISSN: 0038-2469.
PUB. COUNTRY: South Africa
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197812
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19781202

AB Conventional **insulins** contain **impurities** which are immunogenic; these include pancreatic polypeptide (PP), glucagon and somatostatin and intermediates of **insulin** synthesis co-extracted during **purification**. Monocomponent (MC) **insulins** are free of these contaminants. In 49 **insulin**-treated diabetic patients, **antibodies** were found to **insulin** (94%), pro-**insulin** (68%) and PP (68%). **Antibodies** to glucagon and somatostatin were not detected. There was a significantly lower mean

maximum binding and titre of **insulin** and PP **antibodies** and total circulating **insulin** (i.e. **antibody** bound and free) in patients receiving MC **insulin**. In patients treated with MC **insulins** for longer than 2 years there was a significant fall in the mean maximum binding of **insulin** and total serum **insulin**, but no consistent change in diabetes control and daily **insulin** dose. It seems that except in the special instances of fat atrophy, **insulin** allergy and certain cases of **insulin** resistance, there is no need to resort to MC **insulin**.

L36 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1977:562071 CAPLUS
DOCUMENT NUMBER: 87:162071
TITLE: Monocomponent **insulin** and its clinical implications
AUTHOR(S): Schlichtkrull, J.; Brange, J.; Christiansen, A. H.; Hallund, O.; Heding, L. G.; Joergensen, K. H.; Rasmussen, S. Munkgaard; Soerensen, E.; Voelund, A.
CORPORATE SOURCE: Novo Res. Inst., Copenhagen, Den.
SOURCE: Hormone and Metabolic Research, Supplement Series (1974), 5(Radioimmunoassay: Methodol. Appl. Physiol. Clin. Stud.), 134-43
CODEN: HMRSAU; ISSN: 0170-5903
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Conventional **insulin** [9004-10-8] contains varying amts. of contaminating pancreatic proteins which induced **insulin antibodies** in rabbits. These proteins were fractionated and possess proinsulin [9035-68-1] and **insulin**-like immunogenic sites. In patients, conventional mixed-species **insulin** prepns. also induced **antibodies** against non-**insulin**-like antigenic sites present in bovine a-component. Such **antibodies** were not found in patients treated with the same mixed-species prepns. freed from the high-mol.-wt. contaminants. **Purifn**. of pork **insulin** by gel filtration chromatog. in comparison with recrystns. did not result in lower immunogenicity in rabbits whereas the monocomponent (MC-) **insulin** (pork) showed little or no immunogenicity under the same conditions. Three groups of patients who never had received **insulin** were treated, resp., with conventional Lente (mixed beef/pork), pork Lente of com. grade, and Mono-tard, i.e., Lente made of pork MC-**insulin**. The **insulin antibody** levels were followed for about 2 years. Conventional Lente (mixed species) was more immunogenic than the porcine variety. The latter induced significant amts. of **insulin antibodies** in comparison to the monocomponent pork **insulin**, which had little or no immunogenicity, demonstrating the significance of the **impurities**.

L36 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1974:22967 CAPLUS
DOCUMENT NUMBER: 80:22967
TITLE: Glomerular basement membrane of the rabbit kidney on long-term treatment with heterologous **insulin** preparations of different purity
AUTHOR(S): Wehner, H.; Huber, H.; Kronenberg, K. H.
CORPORATE SOURCE: Inst. Pathol., Univ. Tuebingen, Tuebingen, Fed. Rep. Ger.
SOURCE: Diabetologia (1973), 9(4), 255-63
CODEN: DBTGAJ; ISSN: 0012-186X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In rabbits treated 1, 2, 3 or 10 mo. with a highly purified monocomponent **insulin** [9004-10-8] (20 units, 3 times weekly, s.c.), there was no alteration of **antibody** formation and no increased occurrence of

kidney subepithelial basement membrane protuberances. In contrast, administration of **insulin impurities** (high-mol. wt. proteins, proinsulin, **insulin** dimer and intermediates), obtained on **purifn.** of **insulin**, increased the **antibody** titer and induced nodular basement membrane changes in the glomeruli. The high antigenicity of com. available **insulin** prepns. may be due to the presence of **impurities**.